Modeling Cell-Sheets Wound Closure

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Résumé - Abstract: *Nous étudions la validité des modèles de réaction-diffusion de type Fisher-KPP pour la simulation de migration de feuillets cellulaires. Pour cela, nous avons effectué des observations expérimentales sur les monocouches de cellules MDCK. Les videoscopies obtenues sont segmentées et binarisées, permettant d'obtenir avec précision les variations d'aire et les profils de fronts de cicatrice. Nous comparons les variations de fronts calculés à celles des fronts expérimentaux, après une étape de calage de paramètres. Nous concluons que, selon l'existence d'activateurs ou d'inhibiteurs, les équations F-KPP peuvent bien, moyennement ou pas du tout modéliser la dynamique de front de monocouches.*

Mots clés - Key word: *Migration cellulaire, Cicatrisation, monocouche MDCK, inhibiteurs, Propagation de fronts, équations de Fisher et KPP.*

The first decade of the 21th century is witnessing a blowing up of theoretical and computational mathematical papers related to cell dynamics. Of course, living cells obey by nature complex dynamic processes at sub-molecular, molecular, organelle, single-cell and multicellular scales. Very different physics and mathematics fields are involved depending not only on the scale, but also on the biological and physical processes which are under investigation.
*At the multicellular scale, continuum modeling of the coupled bio-chemo-mechanical behavior of complex biological systems has been extensively studied, and not surprisingly, modeling of tumor growth, pattern formation in embryogenesis or wound healing turned out to handle and deal with common mathematical features, among which the lion share is won by partial differential equations, more precisely by the reaction-diffusion ones. This family of equations is well adapted to describe the time and spatial changes occurring within the cell population, and producing migration and proliferation, two of the most important mechanisms during the wound closure. Roughly speaking, diffusion is related to random motility, while reaction is related to proliferation. The reaction-diffusion equations, coupled to visco-elasticity mechanics, account as well for chemotaxis and haptotaxis among other cell movement characteristics, see e.g. [**?**].*
In the present study, we consider a particular yet major aspect of wound healing, namely the one related to the movement of wounded epithelial cell monolayers.
The epithelial monolayer cell population, also referred to as cell-sheet, can be seen as a 2 dimensional structure, although it is well known that apical and basal sites play distinctive important roles during the migration, as well as the substrate itself. Immediately after a wound is created, the cells start to move in order to fill in the empty space. This movement, the wound closure, is a highly-coordinated collective behavior yielding a structured cohesive front, the wound leading edge.
Even though wound closure involves biochemical and biomechanical processes, still far from being well understood, which are distributed over the whole monolayer, much specific attention was paid to the leading edge evolution, seen as the front of a traveling wave of the cell density function.
*It is then very tempting to investigate the ability of simple PDEs which exhibit traveling waves behavior to model the leading edge evolution. The most known one is the Fisher and KPP equation (F-KPP). F-KPP equation is a nonlinear parabolic partial differential equation, introduced in 1937 by Fisher [**?**] and Kolmogoroff-Petrovsky-Piscounoff [**?**] which models the interaction of Fickian diffusion with logistic-like growth terms.*
Let denote by Ω a rectangular domain (typically an image frame of the monolayer), by Γ_D its vertical sides and by Γ_N its horizontal ones.
We assume that the monolayer is at confluence, and consider the cells density relatively to the confluent one. The F-KPP equation then reads

$$\frac{\partial u}{\partial t} = D\Delta u + ru(1-u) \quad \text{over } \Omega \tag{1}$$

One of the main features of the F-KPP equation is that it drives initial conditions u_0 of compact support (e.g. an initial 1-0 step function) to closure (to the stable steady solution $u = 1$) by propagating the front with a constant velocity $V_{th} = 2\sqrt{rD}$ (up to a short transition time). To our knowledge, the first authors to investigate the validity of the F-KPP equation to model the closure of wounded cell-sheets were Maini et al. [?] [?]. Using a 1D F-KPP approximation, experimental leading edge velocities were assumed to be close to V_{th} and were used to fit the diffusion coefficient D given the proliferation rate r (doubling time tables excerpt from published data).
In our case, we perform a parameter identification of the two parameters (r, D), using a 2D simulation of the F-KPP equation, and advanced image processing to minimize the error between computed and biological observed experimental wound closure.

Conclusion : *We show that, for non inhibited wound assays, closure occurs at constant speed of the leading edge, a fact that is commonly shared by biologists and biomathematicians. But we also show that the leading edge may exhibit accelerated profiles, and that when inhibited, then the F-KPP has poor performances in modeling the leading edge dynamics.*

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